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EARLY CHILDHOOD PREDICTORS OF ASTHMA

NOTICE

CHARLES B. SHERMAN,[1,2] TOR D. TOSTESON,[1] IRA B. TAGER,[3] FRANK E. SPEIZER,[1] AND SCOTT T. WEISS[1]

Sherman, C. B. (Pulmonary Div., The Miriam Hospital, Providence, RI 02906), T. D. Tosteson, I. B. Tager, F. E. Speizer, and S. T. Weiss. Early childhood predictors of asthma. *Am J Epidemiol* 1990; 132:83–95.

To investigate potential risk factors for the development of childhood asthma, the authors undertook a longitudinal study using a cohort of 770 children aged 5–9 years from East Boston, Massachusetts, that has been under study since 1975. The disease outcome considered was age at first onset of asthma, as determined by parental or self-reporting of a physician's diagnosis. Potential risk factors were evaluated specifically in relation to their presence antecedent to a diagnosis of asthma. Standardized questionnaires were used to obtain childhood illness histories, environmental exposures, and the asthmatic and atopic statuses of first-degree relatives. Ninety-one cases of asthma were identified from 1975 to 1988 (57 males and 34 females). Significant sex-adjusted relative risk estimates were seen for antecedent pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. Neither bronchiolitis, eczema, croup, personal cigarette smoking, maternal smoking, paternal smoking, nor delivery complications bore an apparent relation to the development of asthma. A history of parental asthma or parental atopy did not significantly alter the sex-adjusted relative risk estimates for pneumonia, bronchitis, hay fever, or sinusitis. These results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences.

asthma; child; genetics; hypersensitivity; respiratory tract infections

A number of studies have been carried out to investigate risk factors for childhood asthma (1–16). Hospital-based and case-control studies have consistently shown that lower respiratory illness (1–6) and atopy (7–10) are associated with asthma in children. Available longitudinal and community-based studies have found associations between perinatal, social, infectious, and allergic exposures and the risk of asthma in children (11–16). Some uncertainty remains, however, as to the identity and causal significance of early childhood predictors for the development of asthma. The present investigation used longitudinal data from a cohort of 5- to 9-year-old chil-

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Abbreviations: FEF_{25-75}, forced expiratory flow from 25 percent to 75 percent of forced vital capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

[1] Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, MA.

[2] Current address: The Miriam Hospital, Providence, RI.

[3] Veterans Administration Medical Center, University of California, San Francisco, CA.

Reprint requests to Dr. Charles B. Sherman, The Miriam Hospital, 164 Summit Avenue, Providence, RI 02906.

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dren with 13 years of follow-up to evaluate the importance of a range of potential risk factors whose assessment was made antecedent to the onset of asthma.

Materials and Methods

Selection of study sample

Details of the characteristics of the study population have been published elsewhere (17). Briefly, a 34 percent random sample was selected from all children 5–9 years of age enrolled in public and parochial schools in East Boston, Massachusetts, in September 1974. Between January and June of 1975, interviewers visited the households of these children and enumerated all household residents. The residents together with the index children comprised the total study population. All members of the study population were screened annually beginning in 1975, with the exception of the second and third screenings (1976 and 1977). The 5- to 9-year-old index children and siblings of the same ages comprised the study population for these analyses. Data collected during the first year (1975) and for 11 consecutive years (1978–1988) were used.

Data collection

Standardized questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history, and household demographics. Questions relating to chronic respiratory symptoms were those proposed by the Division of Lung Diseases of the National Heart, Lung, and Blood Institute (18). At the first screening, separate but similar questionnaires were used for subjects aged less than 10 years and those aged 10 years or older. Beginning with the fourth screening cycle (September 1977–June 1978), a common questionnaire was used for all subjects. Parents answered all questions for children younger than 10 years of age, except for those questions that pertained to the child's smoking history, which were answered by the child during pulmonary function testing (when parents were not present). Children aged 10 or older answered all questions for themselves.

The time periods covered by these questionnaires differed. The initial questionnaire asked about events in the child's life prior to and up to entry into the study; the fourth year questionnaire focused on events for the period between study entry and the fourth year ("gap" years). Thereafter, each annual survey obtained information about events that occurred between annual surveys or between the time the subject was last seen and the current survey. The age at first occurrence of an illness was defined as the age (in years) at the time of the survey in which a positive response was recorded or the age (in years) at the time of the fourth survey for positive responses occurring during the "gap" years.

Ventilatory function was tested using an 8-liter, water-filled, portable recording spirometer (Survey spirometer; Warren Collins, Inc., Braintree, MA) with the subject in the sitting position and without the use of a nose clip. The spirometers were calibrated on a regular basis. Subjects were encouraged to perform FVC maneuvers until five acceptable tracings were obtained or until it became evident that they could not perform adequately. A tracing was considered acceptable if it was at least 4 seconds in duration and reached an asymptote of at least 1 second. All pulmonary function measurements were corrected to body temperature, ambient pressure, and saturation with water vapor at these conditions.

FVC, FEV_1, and FEF_{25-75} were obtained by standard technique (19). FVC, the greatest volume that can be forcefully exhaled from total lung expansion, may be reduced in subjects with restrictive or severe obstructive ventilatory defects. FEV_1 and FEF_{25-75}, measures of airflow, are reduced in obstructive lung diseases. When mean values of these measurements were used, they were obtained as the mean of the best three of five tracings, as recommended by

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the Division of Lung Diseases (18). Mean lung function values were converted into percent predicted values using the nomograms of Dickman et al. (20).

The disease outcome for this investigation was age at first occurrence of a physician's diagnosis of asthma, as reported by the subject or his/her parent. Hay fever, sinusitis, eczema, pneumonia, and bronchitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial or yearly surveys. Smoking statuses of the index children and their parents were determined from the initial or yearly questionnaire responses. Croup and bronchiolitis were defined by the subject's or parent's report of a physician's diagnosis of these illnesses on the initial questionnaire. Age at first occurrence was obtained for these latter variables.

Other exposure variables included delivery complications, parental asthma, and parental atopy. Information on delivery complications ("Were there any problems with him/her at the time of delivery?"—yes or no) was available only on the initial questionnaire. A parental history of asthma was considered present if either parent of the index child reported, at any time during the study period, ever receiving a physician's diagnosis of the condition. Similarly, parental atopy was defined as self-reporting by either parent of a physician's diagnosis of hay fever and/or eczema at any time during the study period.

Follow-up and losses to follow-up

Asthmatics and nonasthmatics were followed for a comparable number of years (9.2 ± 3.0 (standard deviation) vs. 8.9 ± 3.5, respectively; $p = 0.44$). No sex differences in follow-up years were detected. Incident asthmatics, however, were followed for significantly more years than nonasthmatics (9.7 ± 2.5 vs. 8.9 ± 3.5, respectively; $p = 0.04$), possibly reflecting greater personal or parental concern about their illness.

Of the original 770 members of the cohort, 86 (11.2 percent) were lost to follow-up after the initial survey. At the initial survey, 81 of these subjects were identified as nonasthmatic (11.9 percent of 679 never asthmatics) and five subjects were identified as asthmatic (5.5 percent of 91 asthmatics).

Statistical analysis

The overall goal of the analysis was to identify risk factors for the onset of asthma whose occurrence antedated the time ("age") of first diagnosis of asthma. The Cox proportional hazards model with time-dependent covariates and age as the time variable was used for this purpose (21).

This method was selected because it 1) accounts for the variable length of follow-up time available for each subject and 2) permits the use of covariate data that can legitimately change from survey to survey. The second feature was used in the following way to evaluate the relative risk of first onset of asthma: For those childhood illnesses for which age at first occurrence was available, an age-dependent covariate was created with a value of 1 (exposed) for ages greater than the age at first occurrence of the illness and 0 (unexposed) for ages less than or equal to the age at first occurrence of illness. The procedure assured that any observed increase in risk must pertain to antecedent occurrence of the illness. For comparative purposes, a second age-dependent covariate was created with a value of 1 (exposed) for ages greater than or equal to the age at first occurrence of the illness. The observed increase in risk using this covariate pertained to an antecedent *or* concurrent exposure.

The application of the Cox model required determining the age of first onset of asthma, as well as the age of first occurrence of other childhood respiratory illnesses. These determinations were complicated somewhat by the pattern of administration of the questionnaire. In the first

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year of the study, information concerning age of onset was requested whenever an occurrence of illness was reported. Thus, for ages of onset prior to entry into the study, there is a potential recall bias. This was investigated by introducing an age-dependent variable with a value of 1 for ages of onset at or following entry into the study and 0 for ages before entry, and by fitting interaction effects between this variable and the covariates of interest.

The questionnaire administered in the fourth year of the study did not request the age of onset for asthma and other illnesses occurring since the first year of the study. For illnesses occurring in this 2-year "gap," the age of onset was taken to be the age of the child at year 4 of the study. To examine the impact of this procedure, we performed analyses using 1) the age at year 1 of the study for both the covariate illnesses and asthma; 2) the age at year 1 of the study for the covariate illness with the age at year 4 for asthma; and 3) the reverse of the assignments in part 2.

Student's t tests (two-tailed) were used for comparison of mean spirometric values for asthmatics and nonasthmatics. Only the most recent spirometric lung function for each individual was used in the analysis. Chi-square statistics and Fisher's exact test (two-tailed) were used to test for associations between sex and use of medications and hospitalizations for asthmatics.

Results

Characteristics of asthmatics

There were 91 subjects diagnosed as having asthma during the 13 years of the study. Forty-three asthmatics were diagnosed after entry into the study. Male asthmatics exceeded the expected number based on the sex distribution of the study population (asthmatics: 57 (62.6 percent) males and 34 (37.4 percent) females; study population: 402 (52.2 percent) males and 368 (47.8 percent) females; $p < 0.05$).

Asthmatics and nonasthmatics had normal ranges for all spirometric tests analyzed. All of these spirometric comparisons were performed using the most recently available spirometric lung function value for all individuals. Male asthmatics had larger FVC percent predicted values than male nonasthmatics (102.2 ± 1.7 (standard error of the mean) vs. 98.0 ± 0.8; $p = 0.02$), and female asthmatics had lower FEV_1 percent predicted values than female nonasthmatics (100.9 ± 3.1 vs. 110.3 ± 0.9; $p = 0.002$). No statistically significant difference was found for mean age at the time of most recent testing for asthmatics and nonasthmatics. Asthmatics were, however, taller than nonasthmatics at the last visit (63.4 ± 0.7 cm (standard error of the mean) vs. 61.6 ± 0.3 cm, respectively; $p = 0.04$).

Two analyses were undertaken to evaluate the severity of disease in the asthmatics. Asthmatics diagnosed by the first survey (prevalent cases, $n = 48$) were traced in years 4–13 of the study to determine the frequency of a physician's diagnosis of active asthma. Of these 48 prevalent cases, 13 (27.1 percent) reported an asthmatic diagnosis at least once in the 10-year follow-up. As determined by questionnaire, four of the 91 asthmatics (4.4 percent) were hospitalized at the age of asthma occurrence and nine of the total group (9.9 percent) were ever hospitalized for asthma during the 11 subsequent years of the study. A mean of 1.6 ± 1.0 (standard deviation) hospital admissions for asthma was recorded for those hospitalized. Of the female cases, 17.7 percent ($n = 6$) were hospitalized at least once compared with 5.3 percent of the male cases ($n = 3$) ($p = 0.07$). Fifty-six of the cases (61.5 percent) were medicated for asthma at some time during the follow-up period; the mean number of surveys at which medication use was reported among these children was 3.4 ± 2.5 (standard deviation). Females reported having ever used medication (67.6 percent, $n = 23$) more often than males (57.9 percent, $n = 33$), but the difference was not statistically significant.

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Risk factors

The occurrence or presence, at any time during the study, of respiratory illnesses, atopy, personal or secondary cigarette smoke, delivery complications, parental asthma, and parental atopy is shown in table 1 for asthmatics and nonasthmatics. Asthmatics more frequently reported pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy than nonasthmatics. Prevalent and incident asthmatics had similar occurrences of these factors except hay fever, which was found more often in incident asthmatics than in prevalent asthmatics ($n = 26$ (60.5 percent) vs. $n = 16$ (33.3 percent); $p = 0.01$). At the time of entry into the study, prevalent and incident asthmatics had comparable occurrences of these factors (data not shown).

Sex-adjusted relative risks of asthma associated with these antecedent exposures are presented in table 2. Significant relative risk estimates were found for pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy. All other factors studied bore no apparent relation to the development of asthma (table 2). Although the sex-adjusted relative risk estimate associated with personal smoking did not reach statistical significance, it was of the same magnitude as the other significant estimates. Small numbers may explain the lack of statistical significance. Analyses that used antecedent and antecedent-concurrent covariates produced comparable results. Only antecedent covariates were used in analyses to explore possible causal relations.

Effect modification by illness onset before or after entry into the study was analyzed to evaluate potential recall bias. No statistically significant interaction by time

TABLE 1

Potential risk factors for asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Prevalent asthma ($n = 48$)	Incident asthma ($n = 43$)	Nonasthmatics ($n = 679$)	p
	No. (%)	No. (%)	No. (%)	
Lower respiratory illness				
Pneumonia	18 (37.5)	18 (41.9)	91 (13.4)	≤0.001
Bronchitis	20 (41.7)	20 (46.5)	121 (17.8)	≤0.001
Bronchiolitis	—*	1 (2.3)	8 (1.2)	0.59
Atopy				
Hay fever	16 (33.3)	26 (60.5)	108 (15.9)	≤0.001
Eczema	6 (12.5)	9 (20.9)	73 (10.8)	0.12
Upper respiratory illness				
Sinusitis	14 (29.2)	20 (46.5)	100 (14.7)	≤0.001
Croup	5 (10.4)	9 (20.9)	96 (14.1)	0.34
Other factor				
Personal cigarette smoking	10 (20.8)	14 (32.6)	135 (19.9)	0.14
Maternal smoking	34 (70.8)	27 (62.8)	431 (63.5)	0.58
Paternal smoking	26 (54.2)	24 (55.8)	395 (58.2)	0.83
Delivery complications	8 (16.7)	8 (18.6)	92 (13.8)	0.60
Familial factor				
Parental asthma	19 (39.6)	20 (46.5)	178 (26.2)	0.003
Parental atopy	31 (64.6)	31 (72.1)	367 (54.0)	0.03

* No occurrence.

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TABLE 2

Sex-adjusted relative risk of asthma associated with various factors in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Antecedent exposure		Antecedent, concurrent exposure	
	Sex-adjusted relative risk	95% confidence interval	Sex-adjusted relative risk	95% confidence interval
Lower respiratory illness				
Pneumonia	3.77	2.29–6.20	4.42	2.83–6.91
Bronchitis	2.66	1.64–4.31	3.22	2.09–4.97
Bronchiolitis	—*	—*	—*	—*
Atopy				
Hay fever	4.44	2.17–9.08	8.17	4.56–14.64
Eczema	1.39	0.67–2.91	1.68	0.89–3.17
Upper respiratory illness				
Sinusitis	3.60	1.74–7.44	4.33	2.30–8.17
Croup	0.88	0.36–2.16	0.99	0.45–2.14
Other factor				
Personal cigarette smoking	2.29	0.67–7.88	2.82	0.98–8.09
Maternal smoking	1.09	0.68–1.74	1.18	0.76–1.83
Paternal smoking	1.20	0.62–2.31	1.14	0.63–2.06
Delivery complications	1.27	0.74–2.19		
Familial factor				
Parental asthma	1.95	1.29–2.95		
Parental atopy	1.61	1.03–2.50		

* No occurrence.

of entry was found (data not shown). Pneumonia, bronchitis, hay fever, sinusitis, parental asthma, and parental atopy remained the only significant sex-adjusted predictors detected. In addition, the effect of interval assignment for the onset of covariate illnesses and asthma occurring in the "gap" years was analyzed. No significant differences in relative risk estimates for the occurrence of asthma by interval assignments were found (data not shown). Therefore, all further analyses were performed by assigning illness onset in the "gap" years as the age of the child at year 4 of the study.

A proportional hazards model was constructed that included the six sex-adjusted covariates that were found to be significantly associated with asthma (table 3). Bronchitis, hay fever, and parental asthma were the only significant predictors after adjusting for sex and other covariates in the model. Based upon the estimated covariances of the parameter estimates, the correlation between the coefficients was −0.39 for pneumonia and bronchitis, −0.30 for hay fever and sinusitis, and −0.23 for parental asthma and parental atopy.

TABLE 3

Relative risk of asthma associated with significant environmental and familial factors, as estimated by multiple regression, in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Relative risk	95% confidence interval
Sex (male/female)	2.39	1.35–4.23
Pneumonia (yes/no)	1.38	0.67–2.88
Bronchitis (yes/no)	3.62	1.94–6.77
Hay fever (yes/no)	2.92	1.20–7.06
Sinusitis (yes/no)	2.21	0.88–5.52
Parental asthma (yes/no)	2.43	1.38–4.29
Parental atopy (yes/no)	1.44	0.84–2.48

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Figure 1 graphically illustrates the importance of selected predictors to the cumulative incidence of asthma, by age, using parameter estimates from the full data set. Panel A shows the unadjusted Kaplan-Meier estimates (22) of the cumulative incidence function for the cohort. In this plot, 10.6 percent of the population is shown to have developed asthma by age 12. Based on the adjusted model presented in table 3 and assuming no identified risk factors, males had a greater cumulative incidence of asthma than did females by this age (7.2 percent vs. 3.1 percent; panel B). Furthermore, 23.8 percent of males with bronchitis before age 1 but no other risk factors and 10.8 percent of females with a similar respiratory history had asthma by age 12 (panels C and D).

The possibility that sex altered the associations of the individual risk factors and asthma was evaluated (table 4). Females had a greater risk for the occurrence of asthma associated with all individual risk factors except for bronchitis. Statistical significance, however, was detected only for this interaction of sex and parental asthma and atopy.

Two additional analyses were performed to examine the plausibility of a causal relation between asthma and other illnesses. First, four proportional hazards models were constructed that used bronchitis, pneumonia, hay fever, and sinusitis, respectively, as the dependent variable with asthma as one of the independent covariates (table 5). If significant relations were seen in these "reversed" models, it

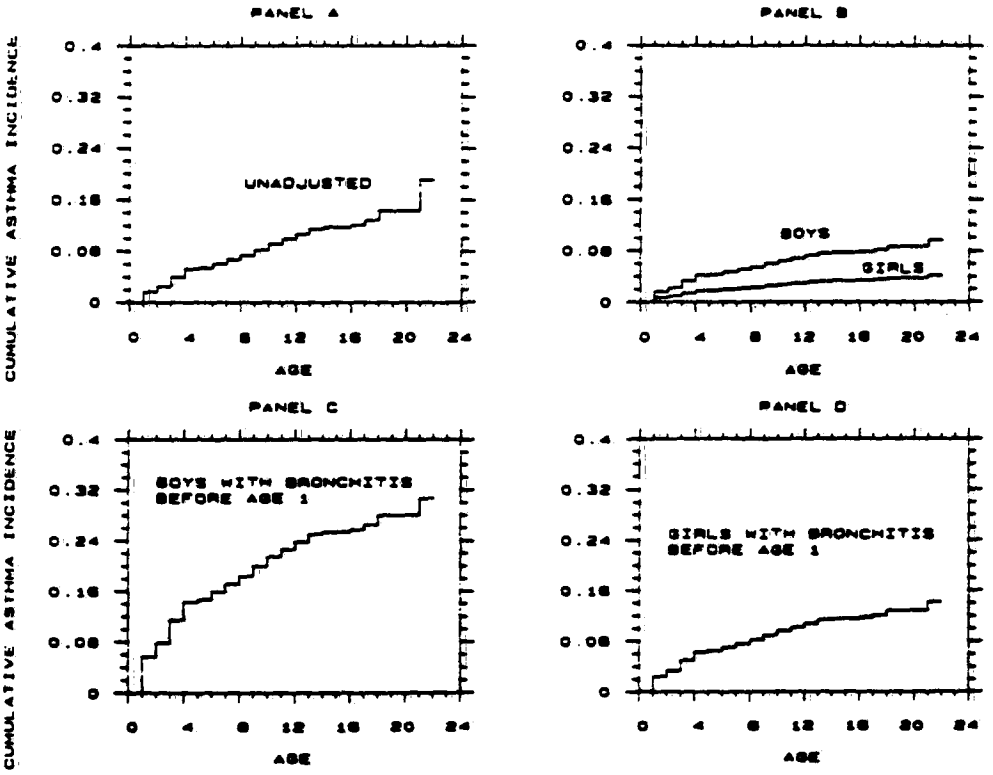

FIGURE 1. Cumulative incidence of asthma, by age, in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988. Panel A, incidence unadjusted for risk factors; Panel B, incidence for children with no risk factors, by sex; Panels C and D, incidence for children who had bronchitis before age 1 year but no other risk factors.

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would suggest that asthma and the illnesses were occurring at about the same time in childhood, rather than sequentially as in a causal model. Asthma was not identified as a significant covariate in models that defined bronchitis or pneumonia as the outcome variable, but it was a statistically significant risk factor for hay fever and sinusitis (table 5).

In the second analysis, simple cross-tabulations were prepared showing the temporal relations between age of onset of asthma and other illnesses for those individuals who developed both. More subjects had the occurrence of bronchitis ($n = 25$ vs. $n = 7$) and pneumonia ($n = 22$ vs. $n = 7$) before, rather than after, the occurrence of asthma, whereas twice as many subjects had the occurrence of hay fever ($n = 11$ vs. $n = 22$) and sinusitis ($n = 10$ vs. $n = 20$) after and not before the occurrence of asthma. Additionally, bronchitis was a significant risk factor for the development of pneumonia, while hay fever and sinusitis were both significant predictors of each other (data not shown). This analysis would suggest that bronchitis and pneumonia as well as hay fever and sinusitis are indistinguishable from one another as predictors.

The risk of asthma associated with any of the individual covariates did not vary by parental asthma or parental atopy (data not shown). However, several interesting trends were seen. The risk of asthma was greatest in subjects with hay fever or sinusitis if they had parental asthma and in subjects with bronchitis or pneumonia if they did not have parental asthma. Additionally, the risk of asthma was greatest in subjects with pneumonia or bronchitis if they had parental atopy.

The effect of age at first occurrence of asthma (age <10 years or ≥10 years) on the relations of the individual risk factors and asthma was assessed (data not shown). This age categorization was chosen because parents answered all questions for children younger than 10 years of age. Again, no

TABLE 4

Interaction of sex and significant environmental and familial factors for asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Factor	Relative risk		p
	Male	Female	
Environmental factor			
Pneumonia (yes/no)	3.03	3.85	0.63
Bronchitis (yes/no)	4.23	2.46	0.35
Hay fever (yes/no)	2.37	4.80	0.24
Sinusitis (yes/no)	1.73	3.83	0.24
Familial factor			
Parental asthma (yes/no)	0.52	3.13	0.0002
Parental atopy (yes/no)	0.57	3.02	0.014

TABLE 5

Sex-adjusted relative risk of upper and lower respiratory illnesses associated with asthma in a longitudinal study of 770 children aged 5–9 years, East Boston, Massachusetts, 1975–1988

Dependent variable	Independent covariates	Relative risk	95% confidence interval
Bronchitis	Sex (male/female)	1.14	0.84–1.56
	Asthma (yes/no)	2.08	0.95–4.51
Pneumonia	Sex (male, female)	1.11	0.78–1.58
	Asthma (yes/no)	1.93	0.88–4.21
Hay fever	Sex (male female)	1.03	0.74–1.43
	Asthma (yes/no)	2.64	1.66–4.18
Sinusitis	Sex (male/female)	1.19	0.84–1.70
	Asthma (yes/no)	2.18	1.34–3.54

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statistically significant difference was found by age of first occurrence of asthma for the relations of any of the individual covariates and asthma. However, point estimates for hay fever and sinusitis were larger before age 10 (9.46 vs. 3.06 and 4.95 vs. 3.10, respectively), while point estimates for bronchitis and pneumonia were greater at or after age 10 (2.46 vs. 2.97 and 3.69 vs. 3.87, respectively).

Discussion

This investigation focused on the quantitative effects of a number of factors that are thought to be associated with and possibly causally related to the occurrence of asthma. Unlike many previous studies, it paid special attention to the temporal relation of the potential risk factors and the occurrence of asthma. The cohort of study children, 5- to 9-year-olds at intake, came from a stable, relatively homogeneous population. The self-report of a physician's diagnosis of asthma determined disease outcome. The asthmatics so identified in this study were similar to other previously described school-aged asthmatics (5, 6, 11–16). They were diagnosed at a young age and had reduced FEV_1 and FEF_{25-75} percent predicted values compared with the nonasthmatics (5, 13, 23). The severity of disease was mild, as is documented by the findings that only 9.9 percent of the asthmatic group were ever hospitalized and 61.5 percent were ever medicated in the 13 years of the study. Most of the prevalent asthmatics (62.5 percent) did not report a further diagnosis of asthma, which is in close agreement with the 65.9 percent rate reported in the National Child Development Study (11) and the 70 percent rate reported from Australia by McNicol and Williams (13).

Sex differences were evident in the asthmatic group. More males than females reported a diagnosis of asthma. Additionally, males were diagnosed more frequently at younger ages and had less extreme disease, as measured by fewer hospitalizations recorded. Clear male/female differences were evident for the effect of asthma on lung function level. Male asthmatics had larger FVC percent predicted and female asthmatics had lower FEV_1 percent predicted than their counterparts. Thus, even after adjusting for differences in height and age, there were male/female differences in level of lung function. The meaning of these differences is unclear and requires further investigation.

The results support the hypothesis that asthma is a multifactor disease whose expression is dependent on both familial and environmental influences. The exact mode of genetic transmission for asthma is still unknown. Autosomal dominance with incomplete penetrance (24) and polygenic inheritance (25) are thought to be the most likely modes of genetic expression. This study was not designed to evaluate specific genetic pathways, but the findings do provide some insight into the interplay between atopy and asthma in first-degree relatives and the development of asthma in childhood. Parental asthma and atopy were both significant bivariate predictors for childhood asthma, which reaffirms the observation that asthma clusters in families (26) and can be inherited as part of a general allergic susceptibility (27, 28). Parental asthma was a stronger predictor than parental atopy, a finding that agrees with previous studies that have shown that parental atopy may enhance the likelihood for the expression of asthma but does not, on its own, impart as great a risk as does parental asthma (25, 29, 30). These data suggest that inheritance of asthma and atopy overlap but are not identical. Females were more likely to develop asthma than males if they had a parental history of asthma or atopy. The significance of this finding is unclear and requires further research.

Four antecedent respiratory illnesses increased the risk of asthma in childhood. Bronchitis, pneumonia, hay fever, and si-

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nusitis all showed significant sex-adjusted relative risk estimates. Bronchitis and hay fever were the most important predictors detected after adjusting for the effects of the other individual covariates. This result, however, must be interpreted with caution, since bronchitis and pneumonia or hay fever and sinusitis are often clinically indistinguishable from each other. Furthermore, bronchitis was predictive of pneumonia and hay fever and sinusitis were each predictive of the other in the Cox models, indicating a high correlation between these variables.

The mechanisms by which bronchitis, hay fever, pneumonia, or sinusitis may cause asthma remain speculative. Bronchitis may act directly by inducing structural changes in the airways (31) or causing alterations in autonomic control of smooth muscle tone (32, 33), leading to increased levels of airway responsiveness and hence to the onset of asthma. In the study population, asthma occurred more often after bronchitis and was not a significant predictor for the occurrence of this illness. Both of these findings would support a possible direct mechanism. A direct pathway for hay fever is less feasible, but indirect mechanisms can be postulated. Hay fever may alter breathing patterns and allow more sensitizing agents (e.g., cold air, aeroallergens) access to the airways, which in turn may increase asthma expression. Alternatively, subjects with a tendency to develop hay fever may also be at risk for developing asthma. Asthma occurred more often before hay fever and was a significant predictor for the occurrence of hay fever. Thus, a direct biologic pathway may be responsible for the development of asthma in nonatopic subjects, while an indirect pathway may be operating in atopic children (34). This hypothesis requires further testing, however, since no direct measures of atopy (i.e., skin testing, immunoglobulin E levels) were obtained in this investigation. Diagnostic misclassification may explain the significance of pneumonia and sinusitis as risk factors for the occurrence of asthma. Of course, subjects with these illnesses may also be indirectly at risk for developing asthma.

A familial predisposition for asthma did not influence the associations between significant covariate predictors and the onset of asthma. Low study power and crude inheritance markers may explain this finding. It is interesting, nonetheless, to examine the parameter estimates from this analysis. Bronchitis had a much greater effect on the development of asthma in subjects without parental asthma. This again supports the concept that injury to the airways, in and of itself, may be sufficient to cause asthma. Hay fever was a stronger predictor in individuals with parental asthma, implying that the expression of asthma and atopy may be interrelated.

Many infectious and environmental factors were not predictive of asthma. It is noteworthy that bronchiolitis and croup were not found to be significant predictors of asthma in this study. These results contrast with those of previously reported studies (3, 4, 9, 35). This finding may reflect a lower occurrence rate and/or a milder expression of these diseases in the East Boston community compared with the other groups studied. An additional possibility is that croup and bronchiolitis are collinear with pneumonia and bronchitis. Alternatively, these respiratory illnesses occurring early in life may be of relevance only for asthma onset at an early age, and the study may lack sufficient power to detect this. Delivery complications had little effect on the risk of asthma and may indicate the imprecise measurement of this variable.

None of the cigarette smoking variables were predictive of asthma. Parental smoking may have resulted in exposure levels too low to increase the risk of asthma. This seems unlikely given previous findings of the relation of parental smoking to wheezing symptoms in children and reduced levels of lung function in asthmatic children (36). Another possible explanation is that

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parental smoking may be not causal but a modifier of the severity of asthma in children with this disorder. In addition, parents in households with wheezing children may have altered their smoking habits. A self-selection factor may explain the lack of significance for personal smoking. Children with hyperresponsive airways may not be able to tolerate the irritating effects of tobacco smoke. Additionally, the low prevalence of personal smoking in this age group may have resulted in reduced statistical power.

Asthma remains a disease that defies definition partially because of the heterogeneity of clinical expression. A self-report of a doctor's diagnosis of asthma, as obtained from a standardized questionnaire, is widely used to identify persons with asthma for epidemiologic research (37–39). Nonetheless, in children, using this definition may result in underdiagnosis of asthma. Taussig et al. (40) concluded from a study of the diagnostic criteria used by Tucson clinicians that considerable overlap of chronic bronchitis and asthma existed. Furthermore, Speight et al. (41) found that asthma was diagnosed in only a small proportion of English schoolchildren with a history of wheezing and bronchial responsiveness to histamine. To the extent that underreporting has occurred in this study, estimates of relative risk for asthma are conservative and are biased toward the null value. A similar argument can be made for self-reporting of a doctor's diagnosis of the other upper and lower respiratory illnesses studied.

Current concepts of asthma as a disease incorporate measures of bronchial hyperresponsiveness. Nonspecific airways responsiveness to cold air challenge has been assessed in a subset of the asthmatics used in these analyses. In a cross-sectional study, Weiss et al. (42) found that 11 of 12 asthmatics with any wheezing in the study year had increased bronchial responsiveness using a cutoff value for cold air challenge of a greater than 9 percent decrease in prechallenge FEV_1/FVC. The one asthmatic not responding had a borderline 8 percent decrease in FEV_1/FVC. Increased responsiveness was also significantly associated with a history of previous asthma. Thus, in this population, the definition of asthma appears to be very sensitive.

The study was designed to avoid several potential biases. Selection bias was not evident, as community and not hospital- or physician-referred participants were enrolled in the study. Preferential recall bias could have been present for those asthmatics diagnosed before entry into the study. Asthmatics or their parents may have been more likely to recall previous respiratory or atopic illnesses at the initial survey. It is unlikely, however, that this could explain our findings, since no effect modification by illness onset before or after study entry was detected. Physicians in the study community could have been more likely to diagnose a child as asthmatic given a parental history of asthma or atopy and frequent episodes of bronchitis, pneumonia, hay fever, or sinusitis. This potential bias could not be directly evaluated.

Associations found in this study met most of the standard epidemiologic criteria for causality (43, 44). An appropriate time sequence of cause before effect was assured by the study definition of exposure and by the use of time-dependent covariates in the analyses. The study results demonstrated consistency with replication. Risk factors for asthma identified by these analyses were similar to those found by several other community-based studies (11–16). Strong associations were found, as is seen by the large relative risk parameter estimates for the significant covariates. The strength of these associations would suggest that bias is less likely to explain the findings. Asthma is a multifactor disease, and therefore specificity of association would not be expected to be upheld. Dose-response relations were not evaluated, and biologic coherence, as previously discussed, remains speculative but plausible.

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In conclusion, several risk factors for the development of childhood asthma have been identified. This study improved upon the methodology used in other population-based studies by ensuring antecedent exposures and by minimizing the effects of selection bias and preferential recall bias.

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